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Original article

Medical treatment of osteoradionecrosis of the mandible by PENTOCLO: Preliminary results

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ABSTRACT

Introduction: Osteoradionecrosis (ORN) is a severe, generally irreversible complication of radiotherapy due to failure of healing. The pentoxifylline-tocopherol combination decreases the superficial fibrosis induced by radiotherapy. Potentiation by Clodronate (PENTOCLO) appears to be effective in ORN of the mandible. The objectives of this study were to evaluate the efficacy and safety of PENTOCLO to treat osteoradionecrosis of the mandible.

Methods: Retrospective study of 27 patients with a mean age of 65 ± 12 years, managed for ORN of the mandible secondary to irradiation for head and neck cancer, treated by the PENTOCLO protocol between January 2010 and March 2011. The primary endpoint was regression of exposed bone until complete healing. Assessment was both clinical (measurement of mucosal ulceration) and radiological (panoramic dental x-rays) before treatment, after antibiotic-corticosteroid combination therapy for one month (M1), and then after 3, 6, 12 months of PENTOCLO.

Results: An improvement of mucosal ulceration was observed in 16/21 patients after 3 months and in 12/17 patients after 6 months of PENTOCLO. Healing was obtained in 16 patients. Median healing time was 82 days (range: 32–266), and was shorter after surgery and radiotherapy (49 days) and longer after chemoradiotherapy (169 days). Radiological healing was achieved later than clinical healing with improvement in 9 out of 20 patients at 3 months. The safety and efficacy of treatment were evaluated by intraoral clinical examination, and assessment of feeding, weight and analgesic consumption. No patient discontinued treatment because of adverse effects.

Conclusion: The PENTOCLO protocol achieved clinical and radiological regression of ORN with, in parallel, a reduction of the indications for major surgery. These preliminary results need to be confirmed by prospective studies comprising quality of life assessment.

1. Introduction

Osteoradionecrosis (ORN) of the mandible is a severe, generally irreversible complication of radiotherapy due to failure of healing. ORN of the mandible occurs several weeks to several years after radiotherapy for head and neck cancer, generally within 3 years [1]. ORN is usually associated with an intraoral mucosal defect and fragile mandibular bone. The clinical presentation varies from patient to patient, but most patients experience intense local pain due to intraoral mucosal break [2].

ORN is an uncommon disease with a highly variable incidence over time and according to various studies (0.4 to 56%) [3], but the current incidence appears to be less than 5% [4]. The mean age of onset is 50 years [5], with a sex-ratio of 1.6 males for 1 female [6]. ORN usually occurs between 4 months and 3 years after radiotherapy, but it has been reported to occur at any time during the patient's life following head and neck radiotherapy [7].

Many factors predispose to the development of the ORN: tumour size and its position in relation to the bone [8], treatment(s) of the tumour (surgery, radiotherapy and chemotherapy), the patient's age and comorbidities. The incidence and severity of ORN increase with poor dental status, dental extraction sites, local trauma and excessive alcohol and tobacco consumption [5,6,9]. The incidence of ORN increases with the total dose of radiotherapy (>66 Gy) [5]. Brachytherapy or surgical resection of mandibular tumour [8] also increases the incidence of ORN.

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Intensity-Modulated Radiation Therapy (IMRT) appears to reduce the incidence of osteoradionecrosis of the mandible [10,11], as new radiotherapy techniques tend to decrease the incidence of ORN as a result of more precise adaptation of the target volume and by individual or even conformal dosimetry.

Many articles have been published on this subject since the first clinical description of osteoradionecrosis in 1922 [12], but the pathophysiology has been only partially elucidated. In 1983, Marx proposed the hypothesis that ORN is due to the triad of hypocellularity, hypoxia and hypovascularity [13]. In 1993, Dambrain emphasized the role of ischemia and infection [14]. Hypovascularity could account for the predominance of ORN involving the angle and body of the mandible, which are supplied exclusively by the inferior alveolar artery, resulting in a more fragile blood supply in the premolar, molar and retromolar sectors [7]. In 2002, Delanian and Lefaix proposed a histopathological definition of ORN, which consists of devitalization of bony trabeculae by destruction of osteocytes and loss of osteoblasts, processes that differ from that observed in osteomyelitis (necrotic acute inflammation of the bone marrow and compact bone) [15]. ORN is the end-result of progressive pathological processes of bone matrix and cell destruction poorly compensated by defective osteogenesis in favour of radiation-induced fibrotic scar tissue [15].

Various definitions have been proposed for ORN, but it can be generally considered to correspond to progressive radiation-induced ischaemic necrosis of the bone associated with soft tissue necrosis spreading a variable distance from the tumour, a recurrence or metastatic disease [16]. As bone tissue absorbs up to 6 times more ionising radiation than the adjacent soft tissues, it is therefore more susceptible [15]. Several authors have tried to define a clinical and radiological classification of ORN. The 3-stage classification proposed by Marx and Myers appears to be the most relevant [17]:

- stage 1: less than 2 mm of exposed bone with or without pain and with radiological signs of diffuse demineralisation;
- stage 2: more than 2 mm of exposed bone;
- stage 3: pathological fracture, oral fistula, fistula or lesion of the inferior border of the mandible.

Management of ORN has not been standardized and is essentially based on symptomatic treatments comprising mouthwashes and repeated courses of antibiotics. Various treatment options have been proposed to manage refractory ORN: drug treatments (vasodilators), hyperbaric oxygen therapy, and sometimes major surgery, with variable results [18].

PENTOCLO therapy is based on the concept of antioxidant and antifibrotic treatment of fibro-atrophy [19]. In the setting of ORN, PENTOCLO is preceded by an initial 4 to 6 weeks of combination anti-inflammatory, antifungal and antibiotic treatment to control local superinfection in the irradiated zone (intraoral exposed bone) responsible for acute episodes of inflammation, especially actinomycosis. The PENTOCLO combination is then initiated to reduce the already constituted fibrotic process (pentoxifylline-vitamin E combination), reduce bone destruction (clodronate) and stimulate healing in combination necrotic zone. Pentoxifylline increases the level of oxygenation in the tissues and vitamin E has an antioxidant action. The pentoxifylline-vitamin E combination significantly decreases radiation-induced fibrosis via a synergistic action [20]. The addition of clodronate inhibits osteoclastic bone destruction [21] (Fig. 1).

Delanian et al. reported that the pentoxifylline-tocopherol combination was not only able to reduce radiation-induced fibrosis [20], but also promoted rapid healing of minimal forms of ORN [9]. Subsequent potentiation with clodronate (PENTOCLO) improved these results in refractory mandibular ORN in a phase II single-centre trial recently published by Delanian et al. [18].

Table 1
Study population.

Characteristics	*n*
Number of patients treated	*n* = 27
Age on inclusion: mean ± standard deviation (range)	65 ± 12 (46–87)
Tumour (n)	
Oral cavity	13
Oropharynx	11
Other	3
TNM (n)	
T1	2
T2	6
T3	6
T4	11
TX	2
N0	8
N1	6
N2	13
M0	27
Treatment (n)	
Radiotherapy alone	1
Concomitant chemoradiotherapy	7
Surgery + radiotherapy alone	15
Surgery + sensitized radiotherapy	4
Mean interval between end of RT-diagnosis of ORN (months)	39 ± 36 (2–122)
Interval between diagnosis of ORN-inclusion in PENTOCLO protocol	
0 to 3 months (*n*)	13
> 3 months (*n*)	13
Mean interval for patients with an interval > 3 months (months)	22.93 ± 18.3 (3–57)
Treatment of ORN prior to PENTOCLO (n)	
Medical	10
Surgery	4
HBO	0
Initial clinical status (n)	
No exposed bone or ulceration	2
Minimal mucosal ulceration	2
Exposed bone < 2 cm	11
Exposed bone 2 to 4 cm	2
Exposed bone > 4 cm or fracture	0
Initial radiological status (n)	
No bone lysis	3
Cortical bone lysis	9
Major bone lysis	10
Fracture	4

ORN: osteoradionecrosis; HBO: hyperbaric oxygen therapy.

The objectives of the present study were to study the efficacy and safety of PENTOCLO therapy for osteoradionecrosis of the mandible in our institution.

2. Patients and methods

2.1. Population

Between January 2010 and March 2011, 27 patients were treated with the PENTOCLO combination for a osteoradionecrosis of the mandible at centre François-Baclesse (CRLCC) and in the head and neck surgery department at the University Hospital of Caen.

This series comprised 22 men and 5 women, with 22 smokers (81%), 8 of whom continued smoking at the time of initiation of treatment. Nineteen patients continued regular alcohol consumption at the time of discovery of their tumour (70%). The mean age on inclusion was 65 (± 12) years (Table 1).

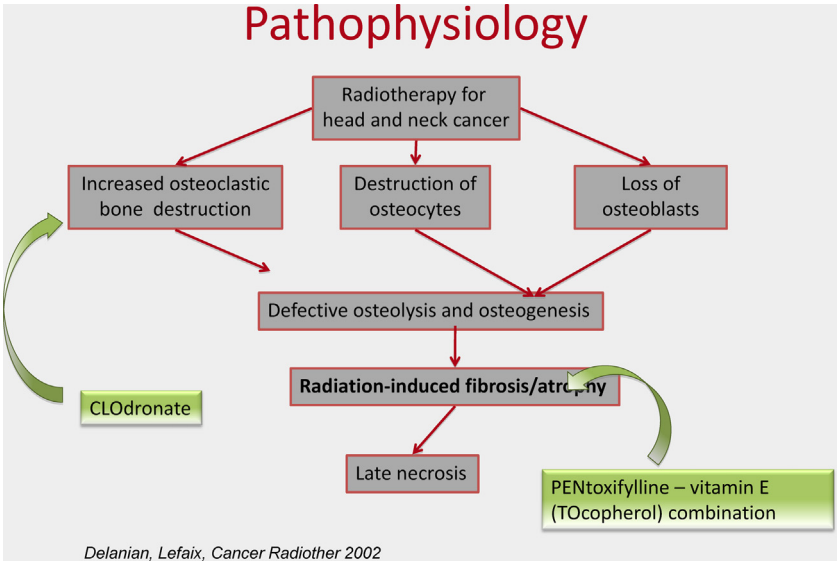

Fig. 1. Pathophysiology of mandibular ORN (according to Delanian and Lefaix [17]).

Thirteen patients were managed for a tumour of the oral cavity, 11 for a tumour of the oropharynx, 2 patients for lymphadenopathy with an unknown primary and one patient for a parotid tumour. The histology was squamous cell carcinoma in all cases except for the parotid tumour (undifferentiated). No active tumour (local recurrence or metastasis) was present at the time of initiation of PENTOCLO.

2.2. Previous radiotherapy

Radiotherapy had been used alone or in combination with chemotherapy and/or surgery. The total dose delivered was 54 to 136 Gy (during two courses of radiotherapy in the same patient) with a median dose of 68 Gy. All patients were treated by photons then electron conformal radiotherapy. No patient was treated by brachytherapy. Only 7 patients developed ORN after a radiotherapy dose of 58 Gy, while 20 cases of ORN occurred after a dose of 68 Gy or more.

2.3. Osteoradionecrosis of the mandible

ORN predominantly affected the body (12 patients) or the angle of the mandible (7 patients) or both (3 patients). The mean length of exposed bone (largest dimension of the lesion) was 1.3 cm (range: 0.1–3 cm). Prior to treatment with PENTOCLO, ORN had been managed by antibiotics in 10 patients, for a mean duration of 21 days, mostly consisting of amoxicillin-clavulanic acid or erythromycin. Four patients had been treated surgically (mandibular resection with or without reconstruction). Hyperbaric oxygen therapy had not been performed in any of the patients of this series.

The mean interval between the end of radiotherapy and the diagnosis of ORN was 39 ± 36 months (range: 2–122 months). The mean RT-ORN interval was 19 months for the 7 patients treated by concomitant chemoradiotherapy, 51 months for the 15 patients treated by adjuvant radiotherapy alone and 23 months for the 4 patients treated by adjuvant sensitized radiotherapy. The patient treated by exclusive radiotherapy presented an RT-ORN interval of 66 months.

ORN secondary to radiotherapy for cancer of the oral cavity was more severe than ORN observed in patients treated for a tumour of the oropharynx, as 4/13 patients had at least 2 cm of exposed bone after treatment of a tumour of the oral cavity versus only 1 patient after treatment of a tumour of the oropharynx.

2.4. PENTOCLO protocol

The first treatment phase, lasting 4 to 6 weeks, was designed to reduce tissue infiltration and consisted of daily treatment with a combination of 2 g of amoxicillin-clavulanic acid, 1 g of ciprofloxacin, 50 mg of fluconazole, 20 mg of prednisone and 20 mg of omeprazole.

The second phase of PENTOCLO treatment was continued until complete healing with a daily dose of 800 mg of pentoxifylline, 1 g of tocopherol, 1600 mg of clodronate 5 days a week from Monday to Friday and 20 mg of prednisone 2 days a week, on Saturday and Sunday. This treatment was administered according to the protocol described by Delanian et al.

2.5. Follow-up

Assessment was performed at a defined time-point, regardless of the duration of treatment. This report presents the preliminary results. The number of patients treated therefore decreased with increasing follow-up.

Patients attended an initial assessment with the same doctor at M0 and then at one month (M1), three months (M3), six months (M6) and twelve months (M12). Clinical assessment comprising intraoral examination and a global assessment (feeding, weight, pain and analgesic consumption) were performed at each visit. Radiological assessment was performed by the same practitioner, based on panoramic dental x-rays and CT scan in 3 cases.

2.6. Statistical analysis

The primary endpoint of the study was the course of intraoral exposed bone related to ORN. This clinical assessment was rated according to stages before (M0) and during treatment (M1, M3, M6, M12) with stage 0 = no exposed bone or ulceration; stage 1 = minimal mucosal ulceration; stage 2 = exposed bone < 2 cm; stage 3 = exposed bone measuring 2 to 4 cm; stage 4 = exposed bone > 4 cm or fracture.

Initial radiological criteria were classified in three stages:

- R0 = no bone lysis;
- R1 = cortical bone lysis;
- R2 = major bone lysis; R3 = fracture.

These criteria were determined subjectively in order to facilitate reproducible interpretation of radiological examinations.

Quantitative variables were expressed as the mean, median and standard deviation and qualitative variables were expressed in terms of improvement, deterioration, stability.

3. Results

3.1. Safety

All patients presented good adherence (100%) to treatment. Safety was acceptable: 16/27 patients were able to receive the complete treatment, while treatment had to be adjusted in 6 patients: 4 for minimal toxicity requiring dose reduction (nausea with clodronate for 3 patients). Two patients immediately started treatment at the second phase as they presented no signs of infection. Two patients had to discontinue treatment for another medical cause related to comorbidities (death in one case and malnutrition in one case). No patient discontinued treatment because of adverse effects.

3.2. Associated sequestrectomies

Twelve (45%) of the 27 patients required one or more outpatient sequestrectomies during treatment, with an average of 2.8 per patient, while no sequestrectomies were performed in 15 patients.

3.3. Local clinical assessment

Only the initial assessment was available for two patients: one patient died 2 months after initiation of treatment (unknown cause), and the other patient developed an intercurrent problem with malnutrition requiring placement of a gastrostomy tube and discontinuation of treatment.

Among the 25 patients evaluated at the time of initiation of the second phase of treatment, 14 (56%) obtained clinical improvement, only 1 patient deteriorated and the other 10 patients remained stable. The mean duration of the first treatment phase was 1.4 months (6 weeks).

Twenty-one patients received the PENTOCLO protocol between the two first assessments (M1-M3): 12 of the 21 cases of ORN were improved, only 1 patient deteriorated and the other 8 patients remained stable (Table 2).

Seventeen patients were treated between the two assessments M3-M6: 8 cases of ORN were improved, while 2 patients deteriorated. At this stage of treatment, between M0 and M6, 12/17 patients had improved (70%) (Fig. 2).

Seven patients were treated between assessments M6-M12, and 4 cases of ORN were improved. All patients obtained clinical improvement compared to the initial assessment at M0: the local status was satisfactory for these 7 patients with ORN only measuring less than 2 cm of exposed bone.

The mean healing time after initiation of treatment was 110 ± 76 days (range: 37–266): 167 days for patients initially treated by concomitant chemoradiotherapy, 49 days for patients treated by adjuvant radiotherapy alone and 101 days for patients treated by adjuvant sensitized radiotherapy. Clinical healing was defined by the absence of mucosal ulceration or exposed bone on examination of the oral cavity.

Overall, 16 (59%) of the 27 patients were clinically healed after an average of 110 days (3.6 months). On subgroup analysis of the 8 patients who continued to smoke at the time of initiation of PENTOCLO therapy, only 3 (37%) obtained mucosal healing versus 11 (58%) in the smoking cessation group. Similarly, the mean healing time for patients not drinking alcohol was 49 days versus 101 days for those who continued to drink.

All of the 6 patients with minimal ORN (stage 0–1) at the initial assessment were healed. Eight of the 14 patients initially presenting exposed bone < 2 cm (stage 2) were healed and only 1 of the 5 patients with more advanced ORN (stage 3–4) was healed.

Table 2
Clinical and radiological course, progressive follow-up.

	Clinical course			
	1 month	Between 1 and 3 months	Between 3 and 6 months	Between 3 and 6 months
Improvement	14	12	8	4
Deterioration	1	1	2	0
Stability	10	8	7	3
Total	25	21	17	7
	Radiological course			
	1 month	Between 1 and 3 months	Between 3 and 6 months	Between 3 and 6 months
Improvement	6	6	1	4
Deterioration	2	2	2	1
Stability	14	12	11	1
Total	22	20	14	6

3.4. Radiological assessment

An initial radiological assessment was performed in 26 of the 27 patients, as one patient died before treatment. Nineteen patients (70%) presented signs of cortical or major bone lysis at this initial assessment.

Panoramic dental x-rays were not performed in 3 patients at the M1 assessment. More than 50% of the 22 cases of ORN evaluated remained stable and 6 were improved. Six out of 20 patients improved between assessments M1 and M3 and 12/20 patients remained stable (Table 2). Six out of 14 patients improved between assessments M0 and M6 and only one patient improved between assessments M3 and M6.

At M6, among the 12 patients with clinical improvement, 5 presented radiological improvement and 2 presented deterioration of the radiological signs. In contrast, at M12, after 12 months of PENTOCLO, 5/7 patients (71%) presented improvement of radiological signs (Fig. 3).

3.5. General clinical assessment

At the initial M0 assessment, mean weight on inclusion was 3 kg (range: 45–85): 65.3 kg for men and 49.3 kg for women. The median weight recorded at each visit was 62 kg.

At the initial assessment, 23 (85%) of the 27 patients had exclusively oral feeding regardless of the stage of ORN, and 3/27 had strictly enteral nutrition (11%). After six months of treatment, 14/17 patients had exclusively oral feeding (82%) and only 1 patient required enteral nutrition (6%). At the fourth assessment, no patient still required enteral nutrition and 5 out of 7 patients ate exclusively by mouth.

At the time of initiation of PENTOCLO, 11 patients presented limited mouth opening limitation; this trismus was improved during treatment in 3 patients.

Initially, one half of patients [13] required analgesics. No change was observed at three months, but, at six months, 9 (53%) of the

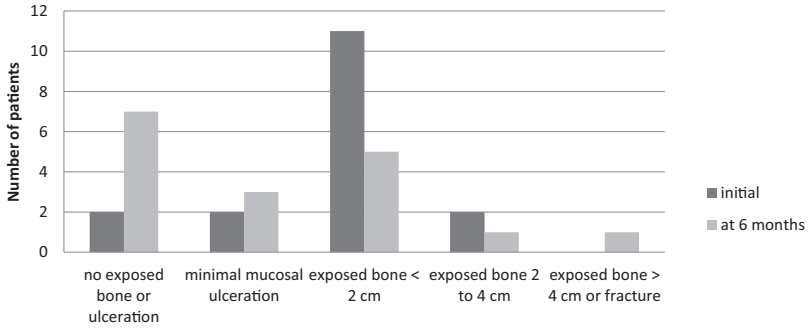

Fig. 2. Clinical course for patients followed for 6 months.

17 patients no longer required any analgesics. After twelve months of treatment, 4 (57%) out of 7 patients no longer required any analgesics.

4. Discussion

4.1. Study population

The mean age of onset of ORN in this series was 64 years, older than the mean age reported in the literature [5]. The usual male predominance was observed (4.4 men for 1 woman). Patients with tumours of the oral cavity and oropharynx were at greater risk of developing osteoradionecrosis of the mandible (7.8) and represented 89% of patients in this series. Osteoradionecrosis was observed after a mean interval of 39 months, i.e. slightly more than 3 years, in line with the data of the literature [1]. Cases of ORN occurring more than 10 years after radiotherapy were observed in this series. Twenty of the 27 patients had received a total irradiation dose greater than 66 Gy, which is known to be a risk factor for ORN [5]. Osteoradionecrosis was observed more rapidly after concomitant chemoradiotherapy than after surgery followed by adjuvant radiotherapy. Concomitant chemotherapy appeared to influence the time to onset of ORN. ORN predominantly involved the body and angle of the mandible (22 out of 27 patients), which can be explained by the blood supply derived exclusively from the inferior alveolar artery [7].

Ongoing smoking at the time of initiation of treatment constituted a risk factor for poor healing of ORN. Smoking was a confounding factor for assessment of healing in this study. Management of ORN consists not only of treatment of eroded bone, but also management of risk factors including alcohol and smoking. The influence of continued alcohol consumption was not evaluated in this study.

Various treatments have been proposed for the management of osteoradionecrosis of the mandible. Conservative medical treatment generally consists of antibiotics and optimized oral hygiene [16], but, when used alone, fails to achieve resolution of ORN in the majority of cases. Marx reported a one-year healing rate of 8% in response to conservative medical treatment in a series of 112 patients [22]. Based on the theory of hypovascularity and hypoxia, hyperbaric oxygen therapy (HBO) has been proposed since 1973 to treat mandibular ORN. However, a prospective randomized double-blind study by Annane et al. showed that HBO did not provide any benefit in the treatment of mandibular ORN with 33% of healing in the placebo group versus 19% in the group treated with HBO [23]. Surgery may be indicated to remove necrotic tissue in order to achieve satisfactory local control of ORN [24], especially for the treatment of ORN refractory to medical treatment [25]. Various techniques can be used, especially local flaps (such as a nasolabial local flap). In the presence of a fracture or threatened fracture, surgery inevitably involves mandibular resection with reconstruction by free bone flap whenever possible. However, these complicated and expensive techniques [26] are only indicated in highly selected patients (good general and vascular status) and must be performed by experienced teams (double surgical team, long operations).

Medical treatment by PENTOCLO has already been demonstrated to be effective for minimal ORN [9] and refractory ORN [21]. The phase II single-centre trial published in 2011 by Delanian et al. showed that PENTOCLO therapy is well tolerated (few adverse effects), allowing mucosal and bone healing of refractory ORN [18], as complete mucosal healing was obtained in every case after a median follow-up of 9 months. Clodronate belongs to the class of biphosphonates that are known to generate the osteochemonecrosis. However, clodronate possesses specific properties, as it is the only non-angiogenic biphosphonate and the only member of this class with osteoblast stimulation properties. Its inhibitory effects on osteoclasts are also 1000 times lower and the concentrations used in the treatment of ORN are lower than those used in other indications [27].

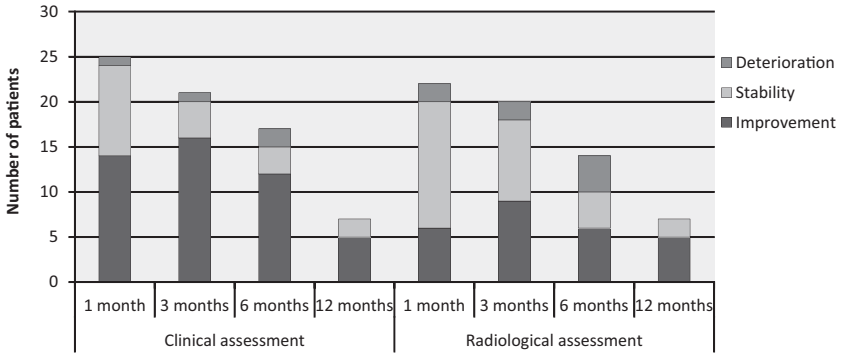

Fig. 3. Clinical and radiological course of ORN.

Clinical improvement was obtained in 70% of cases after 6 months of PENTOCLO in this study. Healing with mucosal recovery was obtained in 60% of cases after a mean interval of 110 days, i.e. less than 4 months, while continuing outpatient sequestrectomies. Longer healing times were observed for patients initially treated by concomitant chemoradiotherapy (167 days, i.e. 118 days longer than for patients treated by surgery and adjuvant radiotherapy alone). This well-tolerated and relatively inexpensive treatment (€200 per month, i.e. €1200 for 6 months) appears to be an attractive alternative for the treatment of all stages of ORN. However, healing time increases with increasing severity of ORN. At centre François-Baclesse, the number of cases of major free bone flap reconstruction surgery in these indications has decreased: an average of 4 free bone flaps per year were performed between 2004 and 2009, while only two cases have required surgery for fractures at the ORN site since the introduction of PENTOCLO therapy.

These preliminary results confirm the results published by Delanian et al. [18]. The lower local control rate could be largely related to continuation of smoking in our series. However, this study presents a number of limitations due to the small sample size and the bias related to missing data and the preliminary data collection, as well as the reader-dependent assessment of radiological examinations.

Orthopantomography, a simple and inexpensive examination, provides essential data for the radiological follow-up of ORN: the state of bone demineralisation, periosteal thickening, Paget-like trabecular structure, and complications (bone sequestra, fracture, signs of osteomyelitis) [14]. However, radiological signs are delayed compared to clinical signs: they are not observed immediately but only after 3 to 6 months, as radiological signs only become apparent after a significant degree of demineralisation (30 to 50%) [4]. Signs of healing on dental panoramic x-rays were also delayed in our study. Radiological signs were improved in only 5 of the 12 patients with clinical improvement after 6 months of PENTOCLO. However, after 12 months of treatment, 5 of the 7 patients who were improved clinically were also improved radiologically.

PENTOCLO therapy was well tolerated and was associated with very good adherence (100%). Treatment changes were minimal and treatment never had to be discontinued because of adverse effects, as in the phase II trial reported by Delanian [18]. PENTOCLO therapy also allowed a reduction of analgesic consumption, although pain can also be related to other factors. Patients did not lose weight and some patients were able to resume oral feeding. Mouth opening was also improved for several patients.

Other treatment modalities are currently under development for the management of mandibular ORN such as hybrid bone substitutes (MBCP granules and total bone marrow transplantation).

5. Conclusion

ORN is a severe complication of radiotherapy related to failure of healing for which no standard treatment is available. ORN is generally observed when irradiation doses to the mandible exceed 66 Gy. Cancers of the oral cavity and oropharynx treated by radiotherapy are at greatest risk of ORN, which usually involves the body or the angle of the mandible. Medical treatment by PENTOCLO appears to be an effective, inexpensive treatment that is almost devoid of adverse effects. It therefore constitutes a good alternative to available treatments for the management of mandibular ORN. Nevertheless, preventive treatment remains essential, based on good oral hygiene, preventive dentistry prior to radiotherapy and alcohol and smoking cessation. New radiotherapy techniques may also reduce the incidence of ORN. The results of this study need to be confirmed by prospective randomized placebo-controlled trials. The present study could be completed by a quality of life assessment in order to optimize the global management of these patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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